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| 10/549,661 | 09/16/2005 | Kyung-Hee Park | YPL-0173 | 2189 |

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| EXAMINER | |
|---|---|
| GOLDBERG, JEANINE ANNE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/549,661 | PARK ET AL. | |
| | Examiner | Art Unit | |
| | JEANINE A. GOLDBERG | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *7,8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,8 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. It is noted that the examiner of the instant application has changed.

2. This action is in response to papers filed June 13, 2008. Claims 7-8, 11 are pending and are under examination on the merits.

3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

4. Any objections and rejections not reiterated below are hereby withdrawn.

a. The double patenting rejection has been withdrawn. The co-pending claims have been amended and no longer require "corresponding." Thus, the rejection in the instant case is moot.

b. The written description rejection has been withdrawn in view of the amendments to the claims to require Korean humans.

c. The 112/1$^{st}$ rejection has been obviated as it applies to any ethnicity of individuals since the claim has been amended to Korean humans. Additionally, the rejection has been obviated as it was applied to variants in linkage disequilibrium. Neither the specification nor the claims contemplate indirectly analyzing the SNP using a SNP or variant in LD with position 101 of SEQ ID NO: 5. Moreover, the response filed June 13, 2008 clearly states that Claim 7 does not recite, as seemingly alleged in the Office Action, determining the sequence of a member of some unspecified genus of sequences, nor does Claim 7 recite an element of “linkage disequilibrium.” Thus, it is clear from applicants specification,

claims and remarks, applicants' claims do not encompass indirectly analyzing the SNP using LD.

d. The 112/2nd rejections have been withdrawn in view of applicants' amendments to the claims.

5. This action contains new grounds of rejection.

### *Election/Restrictions*

6. Applicant's election without traverse of Group II, claims 7-9, and SEQ ID NO:5, having the G allele at the polymorphic site position 101 is acknowledged.

7. It is noted that the subject matter of the nonelected inventions has been cancelled by Applicants.

### *Priority*

8. Acknowledgment is made of applicant's claim for foreign priority based on applications filed in Korea on 2/2/04 and 2/1805. It is noted, however, that a certified copy of each of the foreign applications has not been filed as required by 35 U.S.C. 119(b).

It is noted that a translation of the foreign document has not been received.

### *Claim Rejections - 35 USC § 112 Enablement*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 7-8, 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Teletronics Inc*, 8 USPQ2d 1217 (Fed Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986)) and *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988)).

The breadth of the claims and nature of the invention

Claims 7-8 are drawn to a method of determining risk of developing colorectal cancer, which comprises: determining in a nucleic acid sample from a Korean human the nucleotide base at polymorphic site at position 101 of SEQ ID NO 5 and determining risk of developing colorectal cancer in the human wherein determining the base is G

indicates an increased risk of developing colorectal cancer compared to determining the base is T.

Claim 11 is directed to further comprising determining a genotype in the sample to analyze homozygosity vs herterozygosity.

Guidance in the Specification and Working Examples

The specification teaches studying an association between the position 101 polymorphism in SEQ ID NO: 5 and colorectal cancer (pg 4). The specification teaches performing DNA nucleotide sequence analysis on blood collected from Korean colorectal cancer patients and normal persons (pg 4). The specification teaches in Table 1 that the CCY_041 SNP has an odds ratio of 1.52, a confidence interval of 1.182 and 1.961 and a chi-square value of $4.62 \times 10^{-3}$. The specification teaches in example 1 that the patients were 300 Korean colorectal cancer patients and 300 Korean controls (see page 11). The data provided in Table 1 is not clear whether the statistics is related to the allele frequency data or the genotype frequency. The implications of the statistics are different and the specification does not clearly demonstrate both allele and genotypes are significantly associated with colorectal cancer.

The unpredictability of the art, the state of the prior art, level of skill in the art

While the state of the art and level of skill in the art with regard to correlating polymorphisms with disease state is high, the level of unpredictability in associating any polymorphism with a particular disease state is even higher. The level of

unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

Regarding using polymorphisms to make predictions, the art teaches genetic variations and associations are often irreproducible. Hirschhorn (Hirschhorn et al. Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn suggests a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn et al. caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Quantity of Experimentation

Claims 7-8 are drawn to a method of determining risk of developing colorectal cancer, which comprises: determining in a nucleic acid sample from a Korean human the nucleotide base at polymorphic site at position 101 of SEQ ID NO 5 and determining risk of developing colorectal cancer in the human wherein determining the base is G indicates an increased risk of developing colorectal cancer compared to determining the base is T. The final process step of determining a risk of developing colorectal cancer by determining the G or T allele does not clearly provide any guidance for the

heterozygote individuals who possess both a G and T. Based upon the genotype frequency, more than half of the individuals are heterozygous. Are these individuals at risk for developing colorectal cancer? Claim 11 appears more closely drawn to illustrating that a GT is at increased risk, however the individuals possess a T also. Therefore, it is unpredictable that increased risk can be determined by the mere presence of a G compared to a T because heterozygotes carry both the G and T alleles.

Moreover, the data provided in Table 1 does not clearly provide what results are obtained. The Table contains allele frequencies and genotype frequencies and statistics, however it is unclear what data was analyzed with respect to the statistics. While the data yields a p-value of 0.00462 it is unclear what had been compared, i.e. gentoype or allele frequencies.

## Conclusion

Thus given the claims in an art whose nature is unpredictable, the unpredictability of that art, the research required to define these unpredictable variables, the lack of guidance provided in the specification, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the methods of the claims as broadly written.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 7-8, 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 7-8, 11 are indefinite because the preamble requires a method of determining any risk of developing colorectal cancer, however the final process step is limited to an increased risk. It is unclear whether the method is directed to any risk as suggested by the preamble or only to increased risk as suggested by the final step. The rejection could be easily overcome by amended the preamble to "determining an increased risk of developing colorectal cancer."

### *Conclusion*

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

**/Jeanine Goldberg/**
**Primary Examiner**
September 11, 2008